Open questions

The mysterious mechanism of growth

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If Wolpert's good fairy godmother of science [1] had come to me 15 years ago, I should have asked for the secret of regional specification in animal embryos — how different parts of the body are programmed to form different structures and cell types. But the enormous progress of the last 15 years has meant that we no longer really need her in this area.

Meanwhile, other areas of developmental biology remain mysterious — such as the problem of growth. Although growth is a familiar process, we have no idea why tissues grow or stop growing, how the growth of one tissue or organ is related to that of others, or how the growth of a tissue is related to growth of its constituent cells. Most knowledge of cellular growth concerns the multiplication of tissue culture cells and the role of mitogenic growth factors. But although the laboratory scientist is happiest with cells growing exponentially in a pure culture, cells in the body hardly ever behave this way.

The framework for thinking about growth *in vivo* comes from the researches of Leblond [2] who conducted studies of mitotic and labelling indices of rat tissues during the 1950s and 1960s. He classified tissues into three groups: 'postmitotic', such as neurons and myotubes; 'renewal', such as blood, intestine or skin; and 'expanding', such as liver, salivary glands and pancreas. Renewal tissues show permanent rapid cell division in a germinal region, fed by a relatively small proportion of stem cells; there is thus a continuous flux of new cells as they are produced, divide a certain number of times, differentiate, perform their function, and then are discarded [3]. The curiously named 'expanding' compartment refers to tissues that expand with the animal and then become more or less quiescent. Although the rate of growth is never exponential, it is generally highest in the embryo and falls asymptotically as the tissue nears its final size. Like renewal tissues, most epithelial expanding tissues are divided into structural units, such as kidney tubules or pancreatic acini. Growth of the tissue in the expansion phase involves increases in the number of both cells and structural units. There is also often an increase in cell size and in the proportion of extracellular material, both of which can contribute to overall size.

It is often thought that the final size of body parts is regulated by a systemic negative feedback, but there is evidence for such a mechanism in only a few cases, such as the well-studied examples of liver and kidney regeneration. But most tissues show little response to surgical reduction, even if extirpations are done while the animal and its expanding tissues are actively growing. A half pancreas, for example, continues to grow at about the same rate as before and stops growing before it has caught up with sham-operated controls [4].

Proof of autonomy in tissue growth can best be obtained by grafting young tissues to old animals, or *vice versa*. Twitty [5] showed that eye rudiments transplanted between embryos of different salamander species maintain their usual growth programme, regardless of the species or age of the host. Zinzar *et al.* [6] showed that a mouse embryo gut grows to approximately normal final size when grafted ectopically into a postnatal host. How can the proportions of body parts be maintained if each part grows autonomously and there are no systemic controls to buffer fluctuation?

The case of renewal tissues is even more difficult. Here there is continuous rapid cell division in the germinative regions, such as those of the gastric glands or the intestinal crypts. What mechanism controls the

disposition of cells into growth rather than the differentiation pathway? Presumably it is connected to the mechanism for increasing the number of structural units in the tissue. Careful morphological studies on gastric glands and intestinal crypts have shown that they can form buds which grow and separate from the parent unit in a manner rather reminiscent of the growth of a colonial multicellular organism, such as a hydroid or ascidian [7]. This occurs both during normal growth and following recovery from radiation-induced damage, but nothing is known of its mechanism.

So, if I met the good fairy, I should ask her "What controls the growth of tissues *in vivo*?", and I know the answer would be fascinating.

References

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